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(54) Title: COMBATTING INFECTION IN DELIVERY SYSTEMS

(57) Abstract

The use of taurolidine or taurultam in a method of combatting infection or sepsis in delivery systems is disclosed. In the method, taurolidine or taurultam solutions are used as a temporary seal or flush to prevent or reduce sepsis in delivery systems, such as port systems and/or catheters by which liquids are delivered into a patient.

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"Combating Infection in Delivery Systems"

This invention relates to a method for preventing and combating infection or sepsis in or caused by the use of delivery systems. More particularly it relates to a method for preventing bacterial colonisation in delivery systems which involve the use of catheters and/or reservoirs of liquid for infusions and the resultant sepsis in vivo. In particular it includes a method for reducing or substantially eliminating infection or sepsis in a subcutaneously-implanted access port for drug delivery either by arterial or venous access or peridural administration.

Delivery systems are widely used in medicine as a means for introducing liquid material which might include medicaments, nutrition, or other active agents to a particular locus in a patient. Such systems frequently involve the use of catheters which, for many applications, are surgically or intravenously located and stitched into place for long-term administration of the desired material. Typical systems include central catheters such as may be used for total parenteral nutrition (TPN) used in e.g. short bowel syndrome (for the duration of life), with the risk of sepsis or endocarditis, as well as catheters and drains which are involved in peritoneal dialysis for those with terminal kidney failure, which, if infected, can lead to peritonitis with serious consequences.

One type of delivery system used for some years in the treatment of conditions in humans comprises a reservoir or chamber of small volume subcutaneously-implanted under the fascia having direct access via a catheter to the cardiovascular system. Such systems are known as port systems.

Such systems are often used in the treatment of malignant conditions. The treatment of malignant conditions in humans is becoming increasing sophisticated and the success rate is rising. Oncology has developed to the stage where particular medicaments or combinations of medicaments, e.g. combinations of cytostatics and metastasis inhibitors, in certain doses either as short or long term infusions or bolus injections can be successfully used to target particular types of malignancy and researchers have sought to develop ways by which regimes of chemotherapeutic medication, some of which can be highly toxic, can be administered to a patient at suitable dosage levels over a period of time. The use of i.v.infusion solutions and/or injections of anti-neoplastic agents can damage veins or cause severe complications such as spasm, paravasal necrosis, (thrombo)phlebitis and sepsis.

One type of reservoir includes a penetrable self-sealing membrane and can be filled or topped-up daily in vivo using a specially-designed syringe and needle. Such a reservoir allows slow continuous discharge of medication over a period of time at a dosage level that can be much more closely maintained and regulated then is the case with other forms of oral or parental administration. Because of the reduction in damage to the veins and discomfort of the patient, the technique clearly has a future but a complication which frequently occurs with serious results is that of infection and sepsis.

The reservoir and delivery system itself in this embodiment is usually implanted under local anaesthesia - below the collar bone in a small pocket created surgically on the fascia of the pectoral muscle is one site that has been used. Whilst all the normal precautions to prevent infection can be taken during implantation, it is in recharging of the device that

infection and sepsis is most likely to occur. The system is recharged using the syringe and needle which is passed through the skin and through the self-sealing but penetrable wall of the device. It is difficult to remove all bacteria on the skin prior to recharging and it is inevitable during recharge that some bacteria, for example nosocomial pathogens, and especially resistant pathogens e.g. MRSA or VRE, will be introduced into the system however meticulous the disinfection of the entrance point. Given that therapy is intended to be long-term and that such delivery systems are capable of being recharged up to 2,000 times, there is plenty of opportunity and time for bacterial or fungal infection to take seat and develop into an extremely serious condition. The most common infections are Staphylococcal, such as from multi-resistant *Staphylococcus aureus* (90% penicillin-resistant and methicillin and oxacillin resistant)(MRSA) or from vancomycin-resistant Enterococci (VRE) though other causative organisms such as Streptococci, and rare fungi such as Pseudomonas have also been reported. *Staphylococcus epidermidis* is probably the most frequently reported causative organism.

This situation is exacerbated by the nature of the drug treatment itself. Despite the advances that have been made, oncological chemotherapy still involves treating a patient with materials that are cytotoxic and long-term treatment of this type inevitably weakens the patient's immune system. Anti-neoplastic chemotherapy and radiotherapy lead to immunosuppression in patients. Immunosuppression in patients with malignant tumours leads to reduction of neutrophile granulocytes and neutropenia. Thus, at the same time as an infection may be building up in a patient, his immune system is less capable of dealing with it. The success of anti-neoplastic treatment therefore depends also on the

prophylaxis of nosocomial infections in these high-risk patients. Similar considerations apply to the use of such devices in administering medication for the treatment of AIDS.

Similar considerations can apply to other port systems. Other port systems are known for implantation in the arm, known as a peripheral venoid port catheter, for implantation in the peritoneum, for implantation in the hepatic artery and for spinal or epidural implantation.

It is estimated that such ports or catheter-based delivery systems give rise to infections in up to about 8% of cases. The frequency rate and fatality of sepsis does depend on the catheter site, and some of the risk can be reduced by suitable care of the entrance point. However, the consequences of sepsis are clearly dangerous and costly. Removal or replacement of the delivery system may well have to be carried out operatively, necessitating a further stay in hospital for the patient and further expense. The danger of general systemic infection is real and infection in the delivery system is difficult to treat with systemic antibiotics due to the minimal contact time they allow which is insufficient to combat the colonies of multi-resistant pathogens. In addition to this the possible intensive care costs are substantial. The treatment of a patient with severe sepsis can lead to problems such as ARDS (Adult Respiratory Distress Syndrome) necessitating polypragmasy and polypharmacy. The treatment of nosocomial pneumonia or endocarditis are particularly difficult.

Heart problems in particular can also be caused. If a cava catheter through which delivery of the medicament takes place is intubated into one of the veins returning to the heart, for example the cephalic or subclavian

vein, the femoral vein, one of the jugular veins or the basilic vein near the elbow, it is guided using X-ray during implantation so that the catheter tip is close to the point of entry of the vena cava into the heart. The heart is accordingly often one of the first organs likely to become colonised by bacteria, fungi or viruses and the feared endocarditis septica has been frequently reported. Other complications include vascular lesions, thrombosis, embolism or phlebitis.

Because the infection has its seat of colonised bacteria within the delivery system, this will not be removed simply by treating the patient systemically with antibiotics. Furthermore, attempts have been made to try and apply antibiotics to the delivery system itself, but this gives rise to difficulties because of the development of resistance problems and because of toxic reactions in the bloodstream which arise when the antibiotic is flushed out of the delivery system with isotonic salt solution. This can result in a toxic allergic bolus-type injection of antibiotics which, in severe cases, can result in anaphylactic shock.

In addition, apart from toxicity problems, a further problem once the delivery system is infected is the release by bacteria of bacterial toxins which result in deposit of a fibrin or collagen net on the internal surface of the delivery system. The net can act as support for the growth of residual resistant and untreatable bacteria leading to superinfection and colonisation by resistant pathogens. Fungi and viruses can also be present. Once this happens, the entire delivery system has to be removed immediately and replaced surgically elsewhere under anaesthetic.

Neither can antiseptics be used to rinse or seal the delivery system because they precipitate a toxic

reaction when they are ultimately flushed into the bloodstream. Since anything used to try to remove infection from the delivery system ultimately ends up passing intravenously into the body, the toxicity of general antiseptics completely rules them out of consideration.

We have now found that substantial advantages in the prevention and/or treatment of infection under these circumstances can be obtained if the delivery system is filled, flushed out or sealed when not in use with solutions containing the antibacterial compounds taurultam or taurolidine. These compounds are the only compounds which until now have worked satisfactorily.

These compounds are particularly effective in combating not only infecting bacteria but also in preventing the release of bacterial toxins and as well as inactivating any that may be present. The release of cytokines which activate the coagulation and fibrinolytic systems would be prevented. These compounds are methylol transfer agents and exert their antibacterial activity by reacting with the bacterial cell wall components and forming covalent bonds. Despite, therefore, the possibility of quite lengthy residence time in the delivery system, they have been found not to cause any build-up of resistance. This is not the case with other conventional antibiotics.

In the context of the present situation, this fact that these compounds avoid the development of any resistance is a huge advantage. A solution of taurultam or taurolidine can be used to seal the delivery system between each administration of desired liquid material, such as chemotherapeutic agent or nutrient, or after withdrawal of any blood sample from the reservoir. Should there be any period of time when it is desired

not to use the delivery system for administration of chemotherapeutic or other active or nutritional agent, such as is often the case during the cyclical delivery of chemotherapeutic agents or during total parenteral nutrition, the delivery system can be filled with a taurolidine or taurultam solution to act as an antimicrobial seal. Relatively small volumes (of the order of a few millilitres, e.g. approximately 3ml) of taurolidine or taurultam are required for this. A contact time of about one hour is desirably a minimum, though the seal can be retained for up to twelve hours or more. All of these activities can be carried out without any development of resistance or build up of bacterial toxins such as LPS and exotoxins by resident bacteria. Taurolidine solutions are well tolerated i.v., as there is no toxicity and no side effects have been observed.

Accordingly, viewed from one aspect, we provide the use of taurolidine or taurultam solutions as a temporary seal to prevent or reduce infection and sepsis associated with the use of a delivery system. This is of particular application to the use of catheters.

Viewed from another aspect, the invention comprises the use of taurolidine or taurultam solutions to reduce or prevent infections associated with the use of subcutaneously-implanted delivery systems. These are of particular application to systems which deliver medication from a reservoir via catheter into the cardiovascular system, such as might be used during chemotherapy.

A preferred solution will contain from 0.5 to 3% by weight of taurolidine, or from 1 to 7.5% by weight taurultam, advantageously 3 to 5%, depending on the solubility of the compound. Solutions containing from

1.0 to 2.0% taurolidine are preferred.

The solutions will generally be made up in sterile pyrogen-free water and may also contain, for example, inorganic or other salts or other components to render them isotonic. Parenterally acceptable polyols may, for example, also be present since these have been observed to increase the overall intravenous tolerance of taurolidine. Suitable polyols include carbohydrates, e.g. hexoses such as glucose and fructose (or mixtures of these such as invert sugar), pentoses such as xylose or polysaccharides such as dextran or hydrolysed starch; glycerol and sugar alcohols such as sorbitol, mannitol or xylitol.

The concentration of the polyol can usefully be in the range 3 - 40% by weight. In the case of glucose, the concentration may be in the range 10 - 30% by weight, preferably 20%.

The solutions may also contain polyvinylpyrrolidone (PVP). This may be incorporated into the solutions at a concentration of, e.g. from 4 to 7% by weight. A solution containing 5% PVP is preferred. This assists in solubilising the active substance and contributes also to the oncotic pressure of the solution. The molecular weight of the PVP should not be greater than 30,000 and is preferably less than 10,000, for example between 7000 and 9000. Kollidone 17 as sold by BASF is relatively quickly resorbed and excreted renally.

The use of taurolidine or taurultam has not been found to give rise to any adverse side-reactions and there appear to be no compatibility problems with the plastic materials of which a delivery reservoir or catheter can be made. Indeed, the use of taurolidine appears to have the further advantage that it can reduce the

adhesiveness of fibrin deposits within a plastic delivery system, thus leading to a lower incidence of residual bacteria and infections.

Typical procedures, which should not be considered as limiting, are as follows:

1.) A patient has a Port delivery system comprising a polyurethane chamber of approx. 0.5 cm^3 volume mounted on a small titanium plate implanted in a small pocket in the pectoral muscle. The tip of a catheter of approx 0.3mm diameter leading from it has been intubated into one of the major veins and lies close to the point of entry of the vena cava into the right atrium of the heart. After implantation the chamber was flushed through with 2ml of a sterile 0.9% by weight sodium chloride solution containing 800 I.E. heparin.

The chamber is then filled with approximately 3ml of a 2% by weight Taurolin® (taurolidine) solution (injected into the chamber by special syringe) and the device sealed for up to 12 hours or until whenever chemotherapeutic administration is due.

Prior to introducing a cancer chemotherapeutic agent, for example, the taurolidine solution is rinsed into the bloodstream using saline. Cancer chemotherapeutic agent as desired is then injected into the chamber and is taken into the body over a period of time. Examples of possible such agents include the alkylating agents, such as numistin hydrochloride and cyclophosphamide; antimetabolites such as fluorouracil, cytarabine and methotrexate; anti-tumour antibiotics such as bleomycin sulphate, daunorubicin hydrochloride and idarubicin hydrochloride; alkaloids such as lincristine sulphate and cisplatins such as carboplatin. These agents are administered via the port system in different

formulations for several short-term and long- term infusions or for bolus injections.

After each treatment with medication, or after use of the chamber to withdraw a sample of venous blood, the delivery system is rinsed meticulously with 10 ml of a sterile 0.9% sodium chloride solution. 2 ml of a 2% Taurolin® solution are then introduced into the chamber and the needle removed. The port system is then effectively sealed against microbial infection. After being rinsed with saline, further medication may then be introduced when desired and the cycle repeated.

2.) A patient undergoing total parenteral nutrition is fitted with a central catheter by known techniques. Nutrition is delivered overnight whilst the patient is asleep but during the day the catheter is sealed with approximately 3ml of 2% taurolidine solution. Such an amount and concentration is effective to prevent catheter sepsis, has no side effects when it passes into the body when nutrition recommences possibly several hours later, and has clear advantages over the alternative procedure which involves using large volumes of antibacterial agents mixed with and administered along with the nutrient mix itself.

CLAIMS

1. The use of a solution of taurolidine or taurultam as a temporary seal or flush to prevent or reduce infection and sepsis in liquid delivery systems.

2. Use as claimed in claim 1 wherein the delivery system involves use of a catheter.

3. Use as claimed in claim 1 or claim 2 wherein the delivery system is a subcutaneously implanted delivery system, or port system.

4. Use as claimed in any of claims 1 to 3 wherein the solution contains from 0.5 to 3% by weight of taurolidine or from 1 to 7.5% by weight of taurultam.

5. A method of preventing or reducing infection and sepsis in a liquid delivery system which comprises filling, flushing out or temporarily sealing said system with a solution of taurolidine or taurultam.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUGHAL M. ET AL.: "INFECTED FEEDING LINES" CARE OF THE CRITICALLY ILL, vol. 6, no. 6, 1990, pages 228-231, XP002062743 see page 230, right-hand column, paragraph 4 - page 231, left-hand column, paragraph 2 ---	1,2,5
X	JOHNSTON D.A. ET AL: "TAUROLIN FOR THE PREVENTION OF PARENTERAL NUTRITION RELATED INFECTION: ANTIMICROBIAL ACTIVITY AND LONG-TERM USE" CLINICAL NUTRITION, vol. 12, no. 6, 1993, pages 365-368, XP002062744 see abstract --- -/—	1,2,4,5

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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Inte: onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BLENKHARN J. I.: "THE ANTIMICROBIAL ACTIVITY OF TAUROLIN - A POSSIBLE ADDITIVE FOR PARENTERAL NUTRITION SOLUTIONS" CLINICAL NUTRITION, vol. 6, no. 1, 1987, pages 35-38, XP002062745 see abstract see page 37, left-hand column, paragraph 4 - right-hand column, paragraph 1	1,2,5

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